VOLUME 2

HM 4100 Antimicrobial
EPA Reg. No. 83019-1

Study Title

Dietary Data Discussion to Address Generic Data Requirements

Generic Data Requirements

870.4100 Chronic oral toxicity
870.4200 Carcinogenicity
870.6200 Acute/Subchronic Neurotoxicity
870.7485 Metabolism and pharmacokinetics

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Study Completed On

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Performing Laboratory

n/a

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentially is made for information contained in the above study on the basis of its falling within the scope of FIFRA 10 (d)(1)(A), (B), or (C).

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Company Agent: Bob MacDonald   Date: 12/09/2015

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GOOD LABORATORY PRACTICE STATEMENTS

This study was not conducted in accordance with Good Laboratory Practice Standards, 40 CFR § 160 as it is not a study as defined in the regulation; therefore there was no Study Director or Sponsor.

Submitter: Bob MacDonald Date: 12/09/2015

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Agent for Biosafe, Inc.

DATA DISCUSSION

Supplemental Amendment

The purpose of this supplemental amendment is to provide EPA with the specific support submitted to FDA to obtain the Threshold of Regulation (TOR) Exemption granted by FDA on December 30, 2013.

Through this discussion, including supplemental data (extracted from Form FDA-3480) and additional information on the bonding of the chemical to the substrate, to provide EPA with the necessary data for further consideration in their assessment.

The priority being to reach concurrence with the Agency in affirming that dietary concentrations are below the 200 ppb level, avoiding the need for chronic toxicity testing (870.4100, 870.4200, 870.6200 and 870.7485).

Overview

Organofunctional silane molecules are reactive molecules with a silicon base and oxygen pendent groups that covalently bond to surfaces and allow homopolymerization. These silanol bonds are very stable and among the strongest bonds in chemistry. They form high molecular weight coatings on surfaces and interpenetrating networks (IPNs) within substrates like polymers. Silanes are used to bind the heat shield on the space shuttle and in the adhesives that hold glass in place in high-rise building window walls. Thus they are commercially known for their strong bonding and resistance to leaching.

Although we have taken a worst-case scenario by assuming 100% leaching of the high molecular weight polymer leaving the treated article (knowing it cannot so leach, since it is insoluble in polar and non-polar solvents), we are extending the body systems exposure over the useful life of the food contact article.

Understandingly, there is no scenario where 100% of the cured, high-molecular-weight coating or IPN would leach into the food all at once. The most likely scenario being that some of the silane at the surface of the coating or polymer may be abraded off over a long period of time, but that this would be minimal compared to the remaining silane (1% by weight max) that remains throughout the coating or polymer. Any such polymer abraded would itself be insoluble and would not migrate into the body since it is of a molecular weight and solubility that would make such movement impossible.

By the nature of their addition and reactions in the plastics there is uniform distribution and the available polymeric is insoluble in polar and non-polar solvents. This obviates the possibility of total exposure in a 24 hour period of time and the possibility of 200 ppb being available for contact.

Calculations made were based upon 100% extraction over the life of the treated article. Additional factors were taken into account to address the density of treated material, repeat use of the articles, potential intermittent contact with food and the lifespan of the specific type of article. (see pages 6-8 of 10)

Intended Use Examples

An example of a repeat use article is a polyolefin, nylon or polyurethane used in a commercial food preparation area such as cutting surfaces. Such an article will be used at ambient temperatures not to exceed 100 degrees C. It is estimated that the cutting surface will be used once a day over a five year period.

Another example is a laminate food preparation surface. This article may come in contact with food on an intermittent basis. An estimate of 10 grams of food over 1 square inch 365 times a year. It is estimated that the counter top would have a 10-15 year lifespan.

A third example is a commercial or industrial cooler interior with a 10 year lifetime.

Additional scenarios:
Repeat use activated carbon water filters are prone to growth of bacteria on the surface when they are stored at ambient conditions between uses. Treatment of the activated carbon with HM 4100 Antimicrobial extends the life of the filter by reducing the growth of bacteria on the surface. Activated Carbon Example is included where carbon is used at point of use.

Melamine formaldehyde surfaces for use in food preparation areas. High and Low Density polyethylene or polypropylene laminate used for commercial food preparation and cutting surfaces. Polyurethane clear coat paint or sealant for food contact surfaces. Waxes for food contact surfaces. Spray application using .025% active HM 4100 Antimicrobial for food contact surfaces. Vinyl tubing used for transfer of water or soft drinks.

Specifics are given in each example calculation (see pages 6-8 of 10)

Migration Testing Option

Exposure estimates are calculated assuming a worst case where 100% of HM 4100 Antimicrobial is extracted and makes contact with food. It is assumed that 10 grams of food will contact 1 square inch of surface each time food contacts the surface. The average lifetime of each surface, device or part is proposed in each calculation given.

The density of most polymeric laminates, thin films and coatings range from 0.9-1.2 g/cm3. The density as reported in the literature is used in calculations. These materials range in thickness from .0005 inches to 0.005 inches. All calculations factor in the appropriate thickness. The concentration of HM 4100 Antimicrobial in each material vary depending on quantity that is required for optimum performance. In no case will the concentration exceed 1% HM 4100 Antimicrobial.

Treated materials also include molded, extruded or machined plastic parts that have a maximum of 1% HM 4100 Antimicrobial incorporated through the use of a master batch process. In these cases, HM 4100 Antimicrobial becomes an integral part of the plastic formulation and is distributed evenly throughout the part as an interpenetrating network. In such cases, food only contacts the surfaces and it can be assumed that food only penetrates 1-3 mils of the device or part. This estimate of the penetration thickness will be used in calculations rather than the actual weight of the molded part etc.

Conclusion

HM 4100 Antimicrobial provides permanence by covalently bonding with the matrix forming an interpenetrating network for the substrate being treated. It therefore does not leach over time. All exposure levels were however determined by assuming 100% extraction over the life of the treated article. In all cases DC was calculated to be below 0.1 ppb.

CALCULATIONS

Melamine formaldehyde countertop example:

conversion factor:			1 cc=	.06 in^3	
melamine formaldehyde laminate is .0015 inches thick	1 in x 1 in x .002 in =		0.0015	in^3	
		.0015/.06 =	0.0250	cc	
			0.0250	grams/cc	weight of 1 sq inch using density of 1.0 g/cc
Maximum of HM 4100 in laminate at 1% active.			0.2500	mg of HM 4100	weight of laminate X HM 4100 concentration X 1000 (convert to mgs)
Countertop laminate has 15 year lifetime and is used 3 times a day or		16425	times		simple multiplication
1 in sq contacts 10 grams food each time-total weight of food contacting sur		164250	grams		number of times used X 10 grams of food per square inch.
convertweight of food contact to KG		164.25			Above divided by 1000 to convert to kg
in 15 years extract mg of HM 4100	0.2500	mg			restatement of weight of HM 4100
<M> : mg of HM 4100 /(X) kg of food	0.0015	mg/kg (ppm)			weight of extractant divided by total weight of contacted food
<M> in ppb	1.5221	ppb HM 4100			multiply by 1000 to convert to ppb
DC: ** consumption value 0.05	0.076	ppb HM 4100			multiply above by consumption value
DC Maximum impurity chloropropyltrimethoxysilane	0.0099	ppb			Impurity at 13 % maximum
DC: Maximum impurity methanol	0.0114	ppb			Impurity at 15% Maximum
DC Maximum impurity Dimethyloctadecylamine	0.0023	ppb			Impurity at 3% Maximum

Polypropylene Laminate for Counter Tops and Cutting Boards

polyolefin laminate is .0015 inches thick	1 in x 1 in x .0015 in =		0.0015	in^3	
		.002/.06 =	0.0250	cc	
			0.0022	grams/cc	weight of 1 sq inch using density of 0.89 g/cc
Maximum of HM 4100 in laminate at 1% active.			0.0223	mg of HM 4100	weight of laminate X HM 4100 concentration X 1000 (convert to mgs)
Countertop laminate has 15 year lifetime and is used 3 times a day or		21900	times		simple multiplication
1 in sq contacts 10 grams food each time-total weight of food contacting sur		219000	grams		number of times used X 10 grams of food per square inch.
convertweight of food contact to KG		219			Above divided by 1000 to convert to kg
in 15 years extract mg of HM 4100	0.0223	mg			restatement of weight of HM 4100
<M> : mg of HM 4100 /(X) kg of food	0.0001	mg/kg (ppm)			weight of extractant divided by total weight of contacted food
<M> in ppb	0.1016	ppb HM 4100			multiply by 1000 to convert to ppb
DC: **PP consumption value 0.04	0.0041	ppb			multiply above by consumption value
DC:Maximum impurity chloropropyltrimethoxysilane	0.0005	ppb			Impurity at 13 % maximum
DC:Maximum impurity methanol	0.0006	ppb			Impurity at 15% Maximum
DC:Maximum impurity Dimethyloctadecylamine	0.0001	ppb			Impurity at 3% Maximum

Polyurethane Clear Coat Paint or Sealant for Food Contact Surfaces

clear coat is .0005 inches thick	1 in x 1 in x .0005 in =		0.0005	in^3	
			0.0083	cc	
			0.0088	grams/cc	weight of 1 sq inch using density of 1.05 g/cc
Maximum of HM 4100 in clear coat at 1% active.			0.0875	mg of HM 4100	weight of laminate X HM 4100 concentration X 1000 (convert to mgs)
Clear coat has 7 year lifetime and is used 3 times a day or		7665	times		simple multiplication
1 in sq contacts 10 grams food each time-total weight of food contacting sur		76650	grams		number of times used X 10 grams of food per square inch.
convert weight of food contact to KG		76.65	kg		Above divided by 1000 to convert to kg
in 7 years extract mg of HM 4100	0.0875	mg			restatement of weight of HM 4100
<M> :mg of HM 4100 /(X) kg of food	0.0011	mg/kg (ppm)			weight of extractant divided by total weight of contacted food
<M> in ppb	1.1416	ppb HM 4100			multiply by 1000 to convert to ppb
DC: consumption value 0.05	0.057078	ppb HM 4100			multiply above by consumption value
DC:Maximum impurity chloropropyltrimethoxysilane	0.007420	ppb			Impurity at 13 % maximum
DC:Maximum impurity methanol	0.008562	ppb			Impurity at 15% Maximum
DC:Maximum impurity Dimethyloctadecylamine	0.001712	ppb			Impurity at 3% Maximum

Waxes for Food Contact Surfaces

wax is .0005 inches thick	1 in x 1 in x .0005 in =		0.0005	in3	
			0.0083	cc	
			0.0008	grams/cc	weight of 1 sq inch using density of 0.93 g/cc
Maximum of HM 4100 in clear coat at 1% active.			0.0078	mg of HM 4100	weight of laminate X HM 4100 concentration X 1000 (convert to mgs)
Wax has 1 year lifetime and is used 3 times a day or		1095	times		simple multiplication
1 in sq contacts 10 grams food each time-total weight of food contacting sur		10950	grams		number of times used X 10 grams of food per square inch.
convert weight of food contact to KG		10.95			Above divided by 1000 to convert to kg
In 1 years extract mg of HM 4100	0.0078	mg			restatement of weight of HM 4100
<M> :mg of HM 4100 /(X) kg of food	0.0007	mg/kg (ppm)			weight of extractant divided by total weight of contacted food
<M> in ppb	0.7078				multiply by 1000 to convert to ppb
DC: consumption value 0.05	0.000035	ppb			multiply above by consumption value
DC:Maximum impurity chloropropyltrimethoxysilane	0.000005	ppb			Impurity at 13 % maximum
DC:Maximum impurity methanol	0.000005	ppb			Impurity at 15% Maximum
DC:Maximum impurity Dimethyloctadecylamine	0.000001	ppb			Impurity at 3% Maximum

Activated Carbon Example where carbon is used in potable multiuse water bottle

Assumption that carbon weighs			3 grams			
The max content of HM 4100 is 0.25%		0.0025	%			
The total amount of HM 4100 in carbon block	0.00075	grams ext	0.75	mg ext		multiply weight of carbon by weight percent of HM 4100 active
Amount of treated water gallons				70 gal		
weight of water in kg				266 kg		Convert weight of water multiply gallons by 3.8 kg per gallon
<M> :migration value mg of HM4100 per kg water			0.00281955		ppm	divide total mg of HM 4100 by weight of water passed through carbon
<M> in ppb			2.81954887		ppb	multiply by 1000 to convert to ppb
DC: **Carbon consumption value	0.03		0.08458647		ppb	multiply above by consumption value
DC:Maximum impurity chloropropyltrimethoxysilane			0.01099624		ppb	Impurity at 13 % maximum
DC:Maximum impurity methanol			0.01268797		ppb	Impurity at 15% Maximum
DC:Maximum impurity Dimethyloctadecylamine			0.00253759		ppb	Impurity at 3% Maximum

Activated Carbon Example where carbon is used at point of use

Assumption that carbon weighs			100 grams			
The max content of HM 4100 is 0.25%						
The total amount of HM 4100 in carbon block	0.025	grams ext		25 mg ext		multiply weight of carbon by weight percent of HM 4100 active
Amount of treated water gallons			2400	gal		
weight of water in kg			9120	kg		Convert weight of water multiply gallons by 3.8 kg per gallon
<M> :migration value mg of HM4100 per kg water			0.00274123		ppm	divide total mg of HM 4100 by weight of water passed through carbon
<M> in ppb			2.74122807		ppb	multiply by 1000 to convert to ppb
DC: **Carbon consumption value	0.03		0.08223684		ppb	multiply above by consumption value
DC:Maximum impurity chloropropyltrimethoxysilane			0.01069079		ppb	Impurity at 13 % maximum
DC:Maximum impurity methanol			0.01233553		ppb	Impurity at 15% Maximum
DC:Maximum Impurity Dimethyloctadecylamine			0.00246711		ppb	Impurity at 3% Maximum

Spray Application using .025% active HM 4100

1 liter covers		200 sq ft	
convert to sq inches	28800	sq inches	Convert sq ft to sq inches multiply by 144
1 liter contains grams HM 4100	0.25	grams	
1 sq inch surface contains HM 4100 (mg)	0.00868056	mg	Divide quantity of HM 4100 in grams above by sq inches covered.
apply HM 4100 to food contact surface once a month			
10 grams food contact 1 in2 of surface 3 times a day or		90 times/month	simple multiplication
Total weight of food contacted		900 grams	simple multiplication
convert weight of food to Kg		0.9 kg	divide above by 1000
<M> :mg HM 4100/ kg food	0.00964506	ppm	divide total mg of HM 4100 by weight of food contacted
<M> in ppb	9.64506173	ppb	multiply by 1000 to convert to ppb
DC: **Consumption value 0.01	0.09645062	ppb	multiply above by consumption value
DC:Maximum impurity chloropropyltrimethoxysilane	0.01253858	ppb	Impurity at 13 % maximum
DC:Maximum impurity methanol	0.01446759	ppb	Impurity at 15% Maximum
DC:Maximum Impurity Dimethyloctadecylamine	0.00289352	ppb	Impurity at 3% Maximum

Vinyl Tubing (Tygon) for Transfer of beverages in fountain devices

vinyl tubing inner liner is .008 inches thick	1 in x 1 in x .008 in =	0.008	in^3	
	.008/.06 =	0.1333	cc	
		0.1733	grams/cc	weight of 1 sq inch using density of 1.3 g/cc
Maximum of HM 4100 in tubing at 1% active.		1.7333	mg of HM 4100	weight of Tubing X HM 4100 concentration X 1000 (convert to mgs)
Amount of treated beverage gallons	5475	gal		lifetime 3 years 5 gallons a day
weight of liquid in kg	20805	kg		Convert weight of water multiply gallons by 3.8 kg per gallon
<M> :migration value mg of HM4100 per kg beverage	0.000083		ppm	divide total mg of HM 4100 by weight of water passed through carbon
<M> in ppb	0.08331331		ppb	multiply by 1000 to convert to ppb
DC: **plasticized PVC consumption value 0,03	0.0024994		ppb	multiply above by consumption value
DC:Maximum impurity chloropropyltrimethoxysilane	0.00032492		ppb	Impurity at 13 % maximum
DC:Maximum impurity methanol	0.00037491		ppb	Impurity at 15% Maximum
DC:Maximum Impurity Dimethyloctadecylamine	7.4982E-05		ppb	Impurity at 3% Maximum

*LLDPE film resins' densities range from 0.900 to 0.939 grams per cubic centimeter (g/cm3)
LDPE film resins range from 0.916 to 0.925 g/cm3
MDPE (medium density) resins range from 0.926-0.940 g/cm3
HDPE film resins range from 0.941 to 0.965 g/cm3
PVC tubing density is 1.3 g/cm3
Paraffin wax density 0.93 g/cm3
PP film resins range from 0.890 to 0.905 g/cm3
PVA density 1.19 g/cm3
For rigid polyurethane, I've seen 1.05 g/cm3
** Cf values above were obtained from Table I, Guidance for Industry: Preparation of Premarket Submission for Food Contact Surfaces, Chemistry Recommendations, December 2007. For those materials not listed an estimate was made based on judgement of the market penetration
Notes: consumption factors will be much lower because we will not have 100% percent market penetration.

Sample Impurity Calculations

Calculation of the maximum DC of each potential impurity was conducted by multiplicaiton of the Calculated DC for the respective material by the maximum concentration of each identified impurity
It should be pointed out that none of these impurities are known to survive the process of manufacture of HM 4100

chloropropyltrimethoxysilane is known to have a 13% maximum concnetration in the starting monomer for HM 4100
methanol is known to have a maximum 15% maximum concentration in the starting monomer for HM 4100
is known to have a maximum 3% concentraiton in the starting monomer for HM 4100

Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations

Link:http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081818.htm#aivti

APPENDIX IV. CONSUMPTION FACTORS, FOOD-TYPE DISTRIBUTION FACTORS, AND EXAMPLE OF EXPOSURE ESTIMATE CALCULATIONS

This appendix summarizes packaging data recommended by FDA for evaluating exposure to FCS. An example of how these data are combined with levels of an FCS in food also is presented. A more complete discussion of the source of these data and their use in exposure calculations is presented in Section II.E.

TABLE I - CONSUMPTION FACTORS (CF)

	Package Category	CF	Package Category	CF
A. General	Glass	0.1	Adhesives	0.14
	Metal- Polymer coated	0.17	Retort pouch	0.0004
	Metal- Uncoated	0.03	Microwave susceptor	0.001
	Paper- Polymer coated	0.2	All Polymers[a]	0.8
	Paper- Uncoated and clay-coated	0.1	Polymer	0.4
B. Polymer	Polyolefins	0.35[b]	PVC	0.1
	-LDPE	0.12	-rigid/semirigid	0.05
	-LLDPE	0.06	-plasticized	0.05
	-HDPE	0.13	PET[c,d]	0.16
	-PP	0.04	Other Polyesters	0.05
	Polystyrene	0.14	Nylon	0.02
	EVA	0.02	Acrylics, phenolics, *etc.*	0.15
	Cellophane	0.01	All Others[e]	0.05

[a]Originates from adding CFs for metal-polymer coated, paper-polymer coated, and polymer (0.17 + 0.2 + 0.4 = 0.8).
[b]Polyolefin films, 0.17 (HDPE films, 0.006; LDPE films, 0.065; LLDPE films, 0.060; and PP films, 0.037).
[c]PET-coated board, 0.013; thermoformed PET, 0.0071; PET carbonated soft drink bottles, 0.082; custom PET, 0.056; crystalline PET, 0.0023; PET films, 0.03.
[d]A CF of 0.05 is used for recycled PET applications (see the document entitled "Points to Consider for the Use of Recycled Plastics in Food Packaging: Chemistry Considerations").
[e]As discussed in the text, a minimum CF of 0.05 will be used initially for all exposure estimates.

TABLE II - FOOD-TYPE DISTRIBUTION FACTORS (f_T)

	Package Category	Food-Type Distribution (f_T)			
		Aqueous[(a)]	Acidic[(a)]	Alcoholic	Fatty
A. General	Glass	0.08	0.36	0.47	0.09
	Metal- Polymer coated	0.16	0.35	0.40	0.09
	Metal- Uncoated	0.54	0.25	0.01[(b)]	0.20
	Paper- Polymer coated	0.55	0.04	0.01[(b)]	0.40
	Paper- Uncoated and clay-coated	0.57	0.01[(b)]	0.01[(b)]	0.41
	Polymer	0.49	0.16	0.01[(b)]	0.34
B. Polymer	Polyolefins	0.67	0.01[(b)]	0.01[b]	0.31
	Polystyrene	0.67	0.01[(b)]	0.01[(b)]	0.31
	-impact	0.85	0.01[(b)]	0.04	0.10
	-nonimpact	0.51	0.01	0.01	0.47
	Acrylics, phenolics, *etc.*	0.17	0.40	0.31	0.12
	PVC	0.01[(b)]	0.23	0.27	0.49
	Polyacrylonitrile, ionomers, PVDC	0.01[(b)]	0.01[(b)]	0.01[(b)]	0.97
	Polycarbonates	0.97	0.01[(b)]	0.01[(b)]	0.01[(b)]
	Polyesters	0.01[(b)]	0.97	0.01[(b)]	0.01[(b)]
	Polyamides (nylons)	0.10	0.10	0.05	0.75
	EVA	0.30	0.28	0.28	0.14
	Wax	0.47	0.01[(b)]	0.01[(b)]	0.51
	Cellophane	0.05	0.01[(b)]	0.01[(b)]	0.93

[(a)]For 10% ethanol as the food simulant for aqueous and acidic foods, the food-type distribution factors should be summed.
[(b)]1% or less